
Cancer Clinical Trial Eligibility Criteria: Brain Metastases Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products² regulated by CDER and CBER for the treatment of cancer.^{3,4} Specifically, this guidance includes recommendations regarding the inclusion of patients with brain metastases. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and

¹ This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² For the purposes of this guidance, references to drugs and drug and biological products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

³ Topics of the other three guidances are related to eligibility criteria for patients with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infections; for patients with organ dysfunction or with prior or concurrent malignancies; and regarding minimum age considerations for inclusion of pediatric patients.

⁴ The recommendations in this guidance do not apply to trials designed specifically to assess the safety and efficacy of investigational drugs for the treatment of primary brain cancers (e.g., glioblastoma) or brain metastases.

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lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.^{5,6,7}

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice and should be considered to avoid jeopardizing patient safety.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Every year, approximately 70,000 patients living with cancer in the United States are diagnosed with brain metastases. The incidence of brain metastases is increasing in patients with certain malignancies such as melanoma, lung cancer, and breast cancer. However, patients with brain metastases have historically been excluded from clinical trials due to concerns of poor functional status, shortened life expectancy, or increased risk of toxicity.

Clinical trial eligibility criteria have either excluded all patients with known brain metastases or restricted enrollment to subgroups of those patients, such as those with treated and clinically stable brain metastases. Given the prevalence of brain metastases in patients with cancer, their systematic exclusion from clinical trials may result in the assessment of an investigational drug's efficacy or safety in a trial population that is not fully representative of the patient population that will be prescribed the drug in clinical practice. Designing clinical trials that include patients with brain metastases and including this information in the labeling promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice. Evidence of clinical efficacy in the subset of patients with brain metastases compared to available therapy, with similar efficacy in patients without brain metastases, could serve as the basis for one or more expedited programs (i.e., fast track designation, breakthrough therapy designation, priority review designation, and/or accelerated approval). Labeling claims would depend on the trial design, including the sample size and analysis plan with pre-specified hypothesis, and could be included in an indication statement or clinical studies section.

⁵ Beaver JA, Ison G, Pazdur R, 2017, Reevaluating Eligibility Criteria- Balancing Patient Protection and Participation in Oncology Trials, *NEJM*, 376:1504-1505.

⁶ Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, *JCO*, 35(33): 3737-3744.

⁷ Lin NU, Prowell T, Tan AR, et al., 2017, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology – Friends of Cancer Research Brain Metastases Working Group, *JCO*, 35(33): 3760-3773.

III. RECOMMENDATIONS

Thoughtful consideration should be given to the potential inclusion of patients with brain metastases in cancer clinical trials. Patients with brain metastases should be included in clinical trials in a way that contributes to a greater understanding of the efficacy and safety profile of the investigational drug while maintaining patient safety. Patients with brain metastases should be included in early drug development trials to facilitate the collection of data to inform the development of eligibility criteria in later-phase trials. In cases where there is a strong rationale for exclusion, the rationale should be described in the trial protocol.

The recommendations in this guidance should be carefully considered in the context of disease stage (e.g., newly diagnosed, metastatic, refractory), information on the mechanism of action of the drug, likelihood of central nervous system (CNS) activity based on pre-existing data, known safety profile, available therapies (and risks of forgoing these), and other patient or disease factors that may alter the benefits and risks of exposure to the investigational drug.

To mitigate uncertainties about including patients with brain metastases in clinical trials, consider enrolling these patients in a separate subgroup within the trial. This strategy allows for generation of supportive safety and efficacy data that could be reported and analyzed separately from the more primary restricted population that does not include patients with brain metastases and may avoid the need for amendments to the protocol or informed consent if futility is demonstrated or adverse events are observed in patients with brain metastases. Other strategies to mitigate risks include limiting enrollment of patients with active brain metastases to a specific number, identifying presence or absence of brain metastases as a stratification factor, designing dose-limiting toxicity (DLT) definitions adapted for use in this population, and incorporating early stopping rules for excessive toxicity.

Due to the importance of distinguishing drug-related CNS toxicity from symptoms related to new or progressive brain metastases, patients with treated/stable, active, or leptomeningeal metastases should have CNS imaging at regular intervals. Schedule on-study assessments for CNS disease at the same time points as assessments for systemic disease. Any unscheduled disease assessments (e.g., due to clinical worsening) should include evaluation of both CNS and systemic disease.

The eligibility criteria regarding patients with brain metastases should describe the eligibility for each of the following types of metastases:

- **Treated/stable metastases** -- where patients have received prior CNS-directed therapy for their brain metastases and their CNS disease is stable,
- **Active metastases** -- where patients have new brain metastases or progressive brain metastases that have not been subjected to CNS-directed therapy since documented progression, and
- **Leptomeningeal metastases** -- where patients have metastases in the leptomeningeal space. Leptomeningeal disease (LMD) is a clinical diagnosis that is defined as positive

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cerebrospinal fluid (CSF) cytology or unequivocal radiologic or clinical evidence of leptomeningeal involvement.

A. Recommendations for inclusion of patients with treated/stable brain metastases

- Patients with treated/stable brain metastases should be included in trials unless there is a strong rationale to exclude such patients.
- Inclusion of patients with treated/stable brain metastases should not be dependent on whether the drug's pharmacological properties predict penetration of the blood-brain barrier.
- Patients should be neurologically stable prior to study entry to mitigate the uncertainty of attributing CNS toxicity to the investigational drug or underlying disease. To achieve this, consider limiting enrollment to patients receiving a stable or decreasing corticosteroid dose at the time of study entry.

B. Recommendations for inclusion of patients with active brain metastases

- Patients with active brain metastases should not be automatically excluded from trials and should be included if the treating physician determines that immediate CNS specific treatment is unlikely to be required and:
 - there is a strong rationale for likelihood of CNS activity, or
 - CNS metastases are common in the target population.
- For drugs with known CNS toxicities, exclusion of patients with active brain metastases may be justified, especially early in drug development.

C. Recommendations for inclusion of patients with leptomeningeal metastases

- Patients with LMD should not be automatically excluded from trials and should be included if:
 - the treating physician determines that immediate CNS specific treatment is unlikely to be required,
 - the drug is anticipated to have CNS activity and is relevant for the primary tumor, and
 - there is strong scientific rationale to support the likelihood of benefit, based on pre-existing data.

D. Recommendations for exclusion of patients with brain metastases

- In early clinical development, for drugs with the potential to increase the risk of bleeding, patients with clinically symptomatic hemorrhage on brain imaging or receiving therapeutic anticoagulation should be excluded until

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preliminary evidence of safety is available demonstrating that participants would not be exposed to unreasonable risk.

- For drugs with the potential to lower seizure threshold, patients with a history of seizures should be carefully screened to assess the potential benefits and risks and optimization of their antiepileptic drug regimen. Exclusion of these patients until preliminary evidence of safety is available demonstrating that participants would not be exposed to unreasonable risk may be prudent.
- For drugs with potential cytochrome P450 (CYP) interactions, patients on certain CYP inducing antiepileptic drugs should be considered for exclusion until preliminary evidence of safety is available demonstrating that participants would not be exposed to unreasonable risk.
- For drugs whose efficacy may be compromised by concurrent corticosteroids, patients requiring corticosteroid use that exceeds a prespecified threshold should be considered for exclusion.

E. Baseline CNS screening

One reason providers have been reluctant to perform screening CNS imaging is because detection of an asymptomatic lesion may preclude patient eligibility for a clinical trial. Expanding eligibility to include patients with brain metastases enables baseline imaging to be performed that does not result in automatic exclusion of all patients with brain metastases. Baseline CNS imaging is recommended to determine if eligibility criteria are met:

- in patients with a known history of brain metastases,
- in populations where the risk of brain metastasis is high,
- if there are specific concerns related to inclusion of patients with brain metastases, and
- if an objective of the study is to evaluate the effect of the investigational drug on CNS-related efficacy outcomes.